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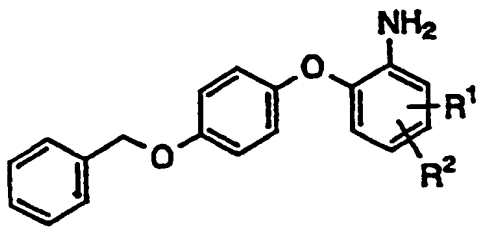
(54) 2-PHENOXYANILINE DERIVATIVES

(57) A 2-phenoxyaniline derivative represented by the formula:



wherein R^1 is a hydrogen atom, an amino group or an $NHCOR^3$ group, R^2 is a halogen atom, an amino group, a cyano group, a C_{1-6} alkyl group, a C_{1-3} perfluoroalkyl group, an $NHCOR^3$ group, a CH_2OR^4 group, an OCH_2R^5 group or a COR^6 group, R^3 is a C_{1-6} alkyl group, R^4 is a hydrogen atom or a C_{1-6} alkyl group, R^5 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-5} aminoalkyl group, a C_{2-7} alkoxycarbonyl group or a carbamoyl group, and R^6 is a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group which is unsubstituted or substituted by a halogen atom, an amino group, a cyano group or a straight or branched C_{1-6} alkyl group; or a pharmaceutically acceptable salt thereof.

EP 0 978 506 A1

Description

TECHNICAL FIELD

[0001] The present invention relates to phenoxyaniline derivatives or pharmaceutically acceptable salts thereof having an inhibitory action on a Na^+/Ca^{2+} exchange system.

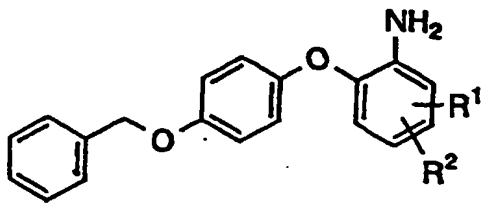
BACKGROUND ART

[0002] Among prior art compounds which inhibit a Na^+/Ca^{2+} exchange system selectively and prevent overload of Ca^{2+} in cells regarded as important in the cell injury mechanism after ischemia or reperfusion, there are known compounds having a quinazoline skeleton as described in Japanese Patent Kokai 7-41465. However, there is no report that the compounds having a phenoxyaniline skeleton as shown in the present invention have an inhibitory action on a Na^+/Ca^{2+} exchange system.

DISCLOSURE OF THE INVENTION

[0003] As a result of extensive researches on the compounds having an inhibitory action on a Na^+/Ca^{2+} exchange system, the present inventors have found that some kind of compounds having a phenoxyaniline skeleton meet said object, and the present invention has been accomplished based on the findings.

[0004] That is, the present invention is directed to a 2-phenoxyaniline derivative represented by Formula (1):



(1)

wherein R^1 is a hydrogen atom, an amino group or an $NHCOR^3$ group, R^2 is a halogen atom, an amino group, a cyano group, a C_{1-6} alkyl group, a C_{1-3} perfluoroalkyl group, an $NHCOR^3$ group, a CH_2OR^4 group, an OCH_2R^5 group or a COR^6 group, R^3 is a C_{1-6} alkyl group, R^4 is a hydrogen atom or a C_{1-6} alkyl group, R^5 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-5} aminoalkyl group, a C_{2-7} alkoxycarbonyl group or a carbamoyl group, and R^6 is a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group which is unsubstituted or substituted by a halogen atom, an amino group, a cyano group or a C_{1-6} alkyl group; or a pharmaceutically acceptable salt thereof.

[0005] Furthermore, the present invention is directed to a pharmaceutical composition containing the above-mentioned compound or the pharmaceutically acceptable salt thereof as an effective component.

[0006] Furthermore, the present invention is directed to a pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases containing the above-mentioned compound or the pharmaceutically acceptable salt thereof as an effective component.

[0007] Furthermore, the present invention is directed to use of the above-mentioned compound or the pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases.

[0008] Furthermore, the present invention is directed to a method for the treatment or prevention of ischemia heart diseases, ischemic cerebral diseases or ischemic renal diseases which includes the step of administering a pharmacologically effective amount of the above-mentioned compound or the pharmaceutically acceptable salt thereof to a human.

[0009] Furthermore, the present invention is directed to a pharmaceutical composition for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation containing the above-mentioned compound or the pharmaceutically acceptable salt thereof as an effective component.

[0010] Furthermore, the present invention is directed to use of the above-mentioned compound or the pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation.

[0011] Furthermore, the present invention is directed to a method for the protection of cells during thrombolytic ther-

apy, angioplasty, bypass operation of coronary artery or organ transplantation which includes the step of administering a pharmacologically effective amount of the above-mentioned compound or the pharmaceutically acceptable salt thereof to a human.

[0012] In the present invention, the halogen atom refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0013] The C_{1-6} alkyl group refers to a straight or branched C_{1-6} alkyl group, and specific examples thereof are a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, a hexyl group and an isohexyl group.

[0014] Specific examples of the C_{1-3} perfluoroalkyl group are a trifluoromethyl group and a pentafluoroethyl group.

[0015] The C_{1-5} aminoalkyl group refers to a straight or branched C_{1-5} aminoalkyl group, and specific examples thereof are an aminomethyl group, a 2-aminoethyl group, a 3-aminopropyl group, a 4-aminobutyl group and a 5-aminopentyl group.

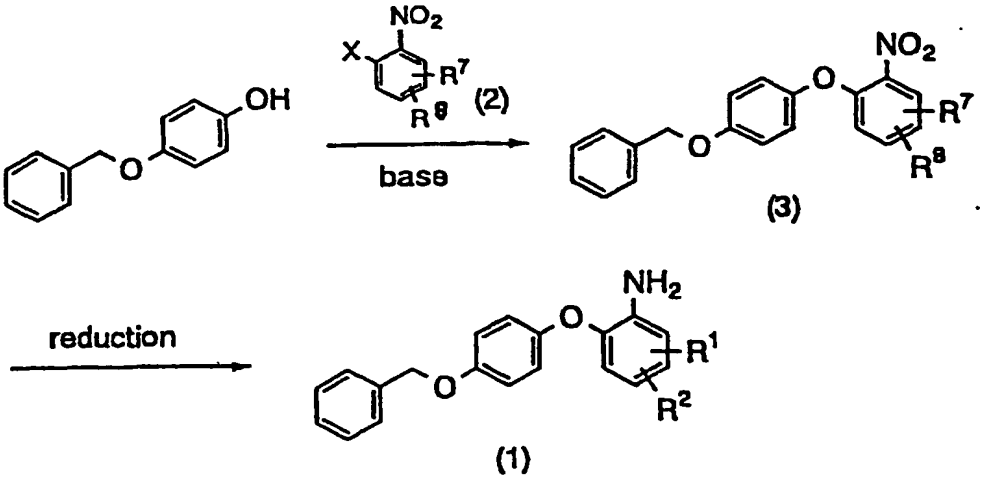
[0016] The C_{2-7} alkoxycarbonyl group refers to a straight or branched C_{2-7} alkoxycarbonyl group, and specific examples thereof are a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, an isobutoxycarbonyl group, a sec-butoxycarbonyl group, a tert-butoxycarbonyl group, a pentyloxycarbonyl group, an isopentyloxycarbonyl group and a hexyloxycarbonyl group.

[0017] Specific examples of the C_{3-8} cycloalkyl group are a cyclopropyl group, a cyclobutyl group, a cyclopentyl group and a cyclohexyl group.

[0018] Preferred phenoxyaniline derivatives of the present invention are compounds of Formula (1) wherein R^1 is a hydrogen atom.

[0019] In the present invention, R^2 is preferably an OCH_2R^5 group (wherein R^5 is a hydrogen atom or a C_{1-6} alkyl group), and more preferably an OCH_2R^5 group (wherein R^5 is a hydrogen atom or a C_{1-2} alkyl group).

[0020] The phenoxyaniline derivatives of the present invention can be prepared, for example, according to the following preparation scheme (wherein R^1 and R^2 are as defined above, R^7 is a nitro group when R^1 is an amino group, or the same substituent as R^1 when R^1 is a substituent other than an amino group, R^8 is a nitro group when R^2 is an amino group, or the same substituent as R^2 when R^2 is a substituent other than an amino group, and X is a fluorine atom or a chlorine atom).



[0021] That is, 4-(benzyloxy)phenol and a compound represented by Formula (2) are reacted in the presence of a base to give a compound represented by Formula (3). Examples of the base to be used herein are organic and inorganic bases such as potassium tert-butoxide, sodium hydroxide or sodium hydride. As the reaction solvent can be used N,N-dimethylformamide or tetrahydrofuran, and the reaction temperature is from room temperature to the reflux temperature.

[0022] Then, the compound represented by Formula (3) is reduced to give a compound of the present invention represented by Formula (1). As the reducing agent can be used herein iron-ammonium chloride, iron-acetic acid, palladium carbon-hydrogen, lithium aluminum hydride, nickel chloride-sodium borohydride, etc. As the reaction solvent can be used herein water, methanol, ethanol, tetrahydrofuran, etc., and they can be used alone or in admixture. The reaction

temperature is preferably from 0°C to the reflux temperature.

[0023] The phenoxyaniline derivative or the pharmaceutically acceptable salt thereof of the present invention is generally administered orally or parenterally to a human.

[0024] In case of oral administration, the phenoxyaniline derivative or the pharmaceutically acceptable salt thereof is mixed with a filler, a disintegrator, a binder, a lubricant, a coating agent, etc., to form granules, powders, capsules or tablets, which then can be administered; and in case of parenteral administration, it can be administered in the form of injectable preparations, drip infusion preparations or suppositories.

[0025] The above-mentioned pharmaceutical preparations can be produced by an ordinary preparation method such as agitation granulation, fluidized bed granulation or disintegration granulation.

[0026] Examples of the filler are mannitol, xylitol, sorbitol, glucose, sucrose, lactose and crystalline cellulose.

[0027] Examples of the disintegrator are low substituted hydroxypropyl cellulose, carboxymethyl cellulose, carboxymethyl cellulose calcium and carboxymethyl cellulose sodium.

[0028] Examples of the binder are methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, gelatin, arabic gum and ethyl cellulose.

[0029] Examples of the lubricant are stearic acid, magnesium stearate and calcium stearate.

[0030] If necessary, an anti-oxidant, a coating agent, a coloring agent, a corrigent, a surface active agent, a plasticizer and others can be added to the pharmaceutical preparations.

[0031] The dose of the effective component of the pharmaceutical preparation in the present invention can be varied depending on the age, body weight or administration route, but it is usually from 0.1 to 1000 mg/day to an adult, which can be administered in a single dose or divided doses.

INDUSTRIAL APPLICABILITY

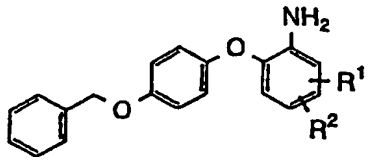
[0032] The compounds of the present invention have an inhibitory action on a Na^+/Ca^{2+} exchange system, thus, they prevent overload of Ca^{2+} in cells, are useful for the treatment or prevention of ischemic heart diseases such as myocardial infarction, ischemic cerebral diseases such as cerebral infarction, or ischemia renal diseases, and further useful for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation.

BEST MODE OF CARRYING OUT THE INVENTION

[0033] The present invention is illustrated in more detail by the following examples and experiments. Furthermore, the structural formula which represents the compounds prepared in Examples 1 to 24 is shown in Table 1.

Table 1

Structural Formula



Example No.	R^1	R^2	
1	H	5-OCH_3	hydrochloride
2	H	5-CH_3	-
3	H	5-CF_3	-
4	H	3-Cl	hydrochloride
5	H	4-CH_3	-
6	H	5-Cl	-
7	H	3-CH_3	hydrochloride
8	3-NH_2	5-CF_3	dihydrochloride
9	H	5-CO-c-C_3H_5	-
10	4-$NHCOCH_3$	5-Cl	hydrochloride
11	H	5-$COCH_3$	-
12	5-NH_2	4-CH_3	-
13	H	5-F	hydrochloride
14	H	3-NH_2	dihydrochloride
15	H	5-CN	hydrochloride
16	3-NH_2	5-CN	dihydrochloride
17	H	5-OCH_2CH_3	hydrochloride
18	H	5-$OCH_2CH_2CH_3$	-
19	H	5-OCH_2CONH_2	hydrochloride
20	H	5-$OCH_2CO_2CH_3$	hydrochloride
21	H	5-CH_2OH	-
22	H	5-CH_2OCH_3	-
23	H	5-$NHCOCH_2CH_2CH_3$	-
24	H	5-$OCH_2CH_2CH_2NH_2$	hydrochloride

Example 1

2-[4-(Benzyloxy)phenoxy]-5-methoxyaniline hydrochloride

[0034]

(1) To a solution of 4-(benzyloxy)phenol (2.00 g, 10 mmol) in N,n-dimethylformamide (20 ml) was added potassium tert-butoxide (1.12 g, 10 mmol), followed by stirring for 10 minutes. To the reaction solution was added 4-chloro-3-nitroanisole (1.88 g, 10 mmol), followed by stirring at 150°C for 6 hours. After allowing to stand overnight, the reaction solution was poured into water and extracted with ethyl acetate. After drying subsequent to washing with water and a saturated aqueous sodium chloride solution, the solvent was evaporated under reduced pressure. The resulting crude crystals were recrystallized from ethanol to give 4-[4-(benzyloxy)phenoxy]-3-nitroanisole (2.13 g).

m.p. 88 - 89.5°C

(2) To a solution of 4-[4-(benzyloxy)phenoxy]-3-nitroanisole (1.23 g, 3.5 mmol) in ethanol (20 ml) were added an iron powder (0.90 g, 16.1 mg-atom) and a solution of ammonium chloride (0.11 g, 2.1 mmol) in water (2 ml), followed by reflux for 3 hours. The insoluble matter was filtered, and the filtrate was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with water, then with a saturated aqueous sodium chloride solution and dried, and thereafter the solvent was evaporated under reduced pressure. The residue was dissolved in a small amount of ethyl acetate, and the resulting solution was, after addition of 4N-hydrogen chloride/acetic acid solution (2 ml), stirred for 30 minutes. The precipitating crystals were collected by filtration and dried under reduced pressure to give the title compound (0.65 g).

m.p. 170 - 170.5°C

[0035] The following compounds of Examples 2 to 16 were synthesized in the same manner as in Example 1, and these instrumental measurement values were shown below.

Example 2

2-[4-(Benzyloxy)phenoxy]-5-methylaniline

[0036]

m.p. 105.5 - 106.5°C

Example 3

2-[4-(Benzyloxy)phenoxy]-5-(trifluoromethyl)aniline

[0037]

m.p. 100 - 101.5°C

Example 4

2-[4-(Benzyloxy)phenoxy]-3-chloroaniline hydrochloride

[0038]

m.p. 176 - 177°C.

Example 5

2-[4-(Benzyloxy)phenoxy]-4-methylaniline

[0039]

m.p. 116.5 - 117.5°C

Example 6

2-[4-(Benzyloxy)phenoxy]-5-chloroaniline

[0040]

m.p. 107 - 108°C.

Example 7

2-[4-(Benzyloxy)phenoxy]-3-methylaniline hydrochloride

[0041]

m.p. 193.5 - 194°C.

Example 8

2-[4-(Benzyloxy)phenoxy-5-(trifluoromethyl)-1,3-phenylenediamine dihydrochloride

[0042]

m.p. 186.5 - 187°C

Example 9

2-[4-(Benzyloxy)phenoxy]-5-(cyclopropylcarbonyl)-aniline

[0043]

m.p. 138 - 140°C.

Example 10

4-Acetamido-2-[4-(benzyloxy)phenoxy]-5-chloroaniline hydrochloride

[0044]

^{1}H-NMR (DMSO-d_6, 200 MHz) δ (ppm); 1.99 (s, 3H), 5.08 (s, 2H), 7.05 (s, 4H), 7.11 (s, 1H), 7.30 - 7.50 (m, 6H), 8.18 (bs, 3H), 9.41 (s, 1H).

Example 11

5-Acetyl-2-[4-(benzyloxy)phenoxy]aniline

[0045]

m.p. 135.5 - 136.5°C

Example 12

4-[4-(Benzyloxy)phenoxy]-6-methyl-1,3-phenylenediamine

[0046]

^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm); 2.03 (s, 3H), 3.50 (bs, 4H), 5.00 (s, 2H), 6.18 (s, 1H), 6.60 (s, 1H), 6.86 (s, 4H), 7.25 - 7.48 (m, 5H).

Example 13

2-[4-(Benzyloxy)phenoxy]-5-fluoroaniline hydrochloride

[0047]

m.p. 176.5 - 177°C.

Example 14

2-[4-(Benzyloxy)phenoxy]-1,3-phenylenediamine dihydrochloride

[0048]

m.p. 173 - 173.5°C.

Example 15

2-[4-(Benzyloxy)phenoxy]-5-cyanoaniline hydrochloride

[0049]

m.p. 170 - 171°C

Example 16

2-[4-(Benzyloxy)phenoxy]-5-cyano-1,3-phenylenediamine dihydrochloride

[0050]

m.p. 160 - 161.5°C

Example 17

2-[4-(Benzyloxy)phenoxy-5-ethoxyaniline hydrochloride

[0051]

(1) To a solution of 4-chloro-3-nitrophenol (5.00 g, 29 mmol) in acetone (50 ml) were added ethyl iodide (4.95 g, 32 mmol) and potassium carbonate (4.37 g, 32 mmol), followed by stirring at room temperature for 20 hours. After filtration of the insoluble matter, the filtrate was subjected to evaporation under reduced pressure to remove the solvent, and the residue was purified by silica gel column chromatography (eluent; chloroform) to give 4-ethoxy-1-chloro-2-nitrobenzene (5.71 g).
(2) The title compound was obtained from 4-(benzyloxy)phenol and 4-ethoxy-1-chloro-2-nitrobenzene in the same manner as in Example 1.

m.p. 164 - 164.5°C.

[0052] The following compounds of Examples 18 to 20 were synthesized in the same manner as in Example 1, and

these instrumental measurement values were shown below.

Example 18

2-[4-(Benzyloxy)phenoxy-5-propoxyaniline

[0053]

m.p. 103 - 103.5°C

Example 19

3-Amino-4-[4-(benzyloxy)phenoxy]phenoxy-acetamide hydrochloride

[0054]

m.p. 198.5 - 199.5°C

Example 20

Methyl 3-amino-4-[4-(benzyloxy)phenoxy]phenoxyacetate hydrochloride

[0055]

m.p. 179 - 180°C.

Example 21

3-Amino-4-[4-(benzyloxy)phenoxy]benzyl alcohol

[0056]

(1) 4-[4-(Benzyloxy)phenoxy]-3-nitrobenzaldehyde was obtained from 4-(benzyloxy)phenol and 4-chloro-3-nitrobenzaldehyde in the same manner as in Example 1(1).

m.p. 111 - 112.5°C.

(2) To a solution of 4-[4-(benzyloxy)phenoxy]-3-nitrobenzaldehyde (2.48 g, 7.1 mmol) in ethanol (100 ml) was added sodium borohydride (0.27 g, 7.3 mmol), followed by stirring at room temperature for 2 hours. The reaction solution was poured into water and extracted with ethyl acetate. The solvent was dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent; chloroform - ethyl acetate (4:1)] to give 4-[4-(benzyloxy)phenoxy]-3-nitrobenzyl alcohol (2.48 g).

m.p. 72 - 73°C.

(3) The title compound was obtained from 4-[4-(benzyloxy)phenoxy]-3-nitrobenzyl alcohol in the same manner as in Example 1(2).

m.p. 128 - 130°C.

Example 22

2-[4-(Benzyloxy)phenoxy]-5-(methoxymethyl)aniline

[0057]

(1) To a solution of 4-[4-(benzyloxy)phenoxy]-3-nitrobenzyl alcohol (9.43 g, 26.9 mmol) in chloroform (60 ml) was added thionyl chloride (2 ml), followed by stirring at room temperature for 6 hours. After allowing to stand overnight,

the reaction solution was washed with water and dried, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent; hexane - chloroform (1:1)] to give 4-[4-(benzyloxy)phenoxy]-3-nitrobenzyl chloride (7.63 g).

m.p. 106 - 107°C.

(2) 60% Oily sodium hydride (0.22 g, 5.5 mmol) was added to methanol (50 ml) under ice-cooling, and after stirring at room temperature for 30 minutes, 4-[4-(benzyloxy)phenoxy]-3-nitrobenzyl chloride (1.00 g, 2.7 mmol) was added thereto, followed by stirring for 3 hours. The reaction solution was poured into water and extracted with ethyl acetate. After drying, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography [eluent; hexane - chloroform (1:1)] to give 1-[4-benzyloxy)phenoxy]-4-(methoxymethyl)-2-nitrobenzene (0.92 g).
(3) The title compound was obtained from 1-[4-(benzyloxy)phenoxy]-4-(methoxymethyl)-2-nitrobenzene in the same manner as in Example 1(2).

m.p. 79.5 - 81°C.

Example 23

N-[3-Amino-4-[4-(benzyloxy)phenoxy]phenyl]-butyramide

[0058]

(1) To a solution of 4-chloro-3-nitroaniline (3.45 g, 30 mmol) in chloroform (100 ml) was added butyric anhydride (5 ml), followed by stirring at room temperature for 2 hours. After allowing to stand overnight, a saturated aqueous sodium carbonate solution was added, followed by stirring for 30 minutes. The organic layer was separated and dried, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography [eluent; hexane - chloroform (1:1)] to give N-(4-chloro-3-nitrophenyl)butyramide (4.66 g).
(2) The title compound was obtained from 4-(benzyloxy)phenol and N-(4-chloro-3-nitrophenyl)-butyramide in the same manner as in Example 1.

m.p. 122.5 - 123.5°C.

Example 24

3-[3-Amino-4-[4-(benzyloxy)phenoxy]phenoxy]-propylamine hydrochloride

[0059]

(1) To a solution of 4-chloro-3-nitrophenol (5.00 g, 29 mmol) in N,N-dimethylformamide (100 ml) were added N-(3-bromopropyl)phthalimide (9.27 g, 35 mmol) and potassium carbonate (4.93 g, 36 mmol), followed by stirring at 60°C for 6 hours. After allowing to stand overnight, the reaction solution was poured into water, and the insoluble matter was collected by filtration and washed with ethyl acetate and dried under reduced pressure to give N-[3-(4-chloro-3-nitrophenoxy)propyl]phthalimide (7.78 g).
(2) N-[3-[4-[4-(Benzyloxy)phenoxy]-3-nitrophenoxy]propyl]phthalimide was obtained from 4-(benzyloxy)phenol and N-[3-(4-chloro-3-nitrophenoxy)propyl]phthalimide in the same manner as in Example 1(1).

m.p. 140 - 141°C.

(3) To a solution of N-[3-[4-[4-(benzyloxy)phenoxy]-3-nitrophenoxy]propyl]phthalimide (2.06 g, 3.9 mmol) in methanol (60 ml) was added hydrazine monohydrate (2 ml), followed by stirring for 3 hours. After allowing to stand overnight, the reaction solution was poured into water and extracted with chloroform. After drying, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in a small amount of ethyl acetate. To this solution was added 4N hydrogen chloride/ethyl acetate solution (2 ml), followed by stirring at room temperature for 30 minutes. The precipitated crystals were collected by filtration and dried to give 3-[4-[4-(benzyloxy)phenoxy]-3-nitrophenoxy]propylamine hydrochloride (1.42 g).

m.p. 179 - 181°C.

(4) The title compound was obtained from 3-[4-(benzyloxy)phenoxy]-3-nitrophenoxy]propylamine hydrochloride in the same manner as in Example 1(2).

^{1}H-NMR (DMSO-d_6, 200 MHz) δ (ppm); 2.02 (quint, J=6 Hz, 2H), 2.94 (sext, J=6 Hz, 2H), 4.00 (t, J=6 Hz, 2H), 5.06 (s, 2H), 6.60 (dd, J=2, 9 Hz, 1H), 6.76 (d, J=9 Hz, 1H), 6.88 (d, J=2 Hz, 1H), 6.92 - 7.08 (m, 4H), 7.28 - 7.50 (m, 5H), 8.09 (bs, 3H).

Experiment

Inhibitory Action on a Na^+/Ca^{2+} Exchange System using Myosarcolemmal Vesicles

[0060] Sarcolemmal vesicles which were prepared from the removed dog ventricular muscles by referring to the method described in the literature (L. R. Jones, Methods, Enzymol., 1988, 157, pp. 85) were used.

[0061] A Na^+/Ca^{2+} exchange activity using the sarcolemmal vesicles was measured by referring to the method described in the literature (K. D. Philipson, et al., J. Biol. Chem., 1980, 255, pp. 6880). First, the sarcolemmal vesicles were suspended in a sodium-containing solution [160 mM sodium chloride, 20 mM Tris-hydrochloric acid (pH 7.4)] to make up to a protein concentration of 1.5 mg/ml, and allowed to stand for an hour to load Na^+ in the sarcolemmal vesicles. To 2.5 μl of the sarcolemmal vesicles was added 125 μl of a [^{45}Ca]-calcium chloride solution [20 μM [^{45}Ca]-calcium chloride, 160 mM potassium chloride and 20 mM Mops-Tris (pH 7.4)], and after 10 seconds, 900 μl of an ice-cooled lanthanum chloride solution [10 mM lanthanum chloride, 160 mM potassium chloride and 20 mM Mops-Tris (pH 7.4)] was added. The sarcolemmal vesicles were recovered on a nitrocellulose filter by suction filtration and washed three times with 900 μl of a lanthanum chloride solution. The concentration of Ca^{2+} uptake in the sarcolemmal vesicles was determined by measuring a ^{45}Ca radioactivity by a scintillator. In addition, a Na^+/Ca^{2+} exchange activity-independent Ca^{2+} uptake in the sarcolemmal vesicles was determined by carrying out the same procedure using a potassium-containing solution [160 mM potassium chloride, 20 mM Tris-hydrochloric acid (pH 7.4)] instead of the sodium-containing solution.

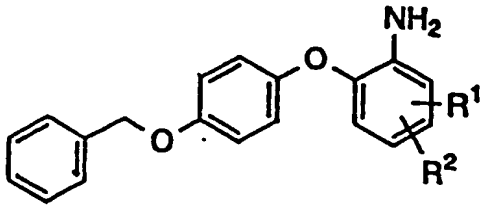
[0062] The test compound was used as a dimethyl sulfoxide solution thereof, and its inhibitory effect was evaluated in comparison with the vehicle-treated group. The IC_{50} value was determined from a dose inhibition curve of the test compound by using the minimum square method. The results are shown in Table 2.

Table 2

Test Compounds	IC_{50} (μM)
1	1.1
14	8.2
17	2.5
19	14.0
20	2.8

Claims

1. A 2-phenoxyaniline derivative represented by Formula (1):



(1)

wherein R^1 is a hydrogen atom, an amino group or an $NHCOR^3$ group, R^2 is a halogen atom, an amino group, a

cyano group, a C_{1-6} alkyl group, a C_{1-3} perfluoroalkyl group, an $NHCOR^3$ group, a CH_2OR^4 group, an OCH_2R^5 group or a COR^6 group, R^3 is a C_{1-6} alkyl group, R^4 is a hydrogen atom or a C_{1-6} alkyl group, R^5 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-5} aminoalkyl group, a C_{2-7} alkoxycarbonyl group or a carbamoyl group, and R^6 is a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group which is unsubstituted or substituted by a halogen atom, an amino group, a cyano group or a C_{1-6} alkyl group; or a pharmaceutically acceptable salt thereof.

2. The 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to Claim 1, wherein R^1 in Formula (1) is a hydrogen atom.

3. The 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to Claim 1, wherein in Formula (1) R^1 is a hydrogen atom and R^2 is an OCH_2R^5 group in which R^5 is a hydrogen atom or a C_{1-6} alkyl group.

4. A pharmaceutical composition containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.

5. The 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 for use as a pharmaceutically active component.

6. An inhibitor of a Na^+/Ca^{2+} exchange system containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.

7. A pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.

8. Use of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 for the manufacture of a pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases.

9. A method for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases which includes the step of administering a pharmacologically effective amount of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 to a human.

10. A pharmaceutical composition for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.

11. Use of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 for the manufacture of a pharmaceutical composition for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation.

12. A method for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation which includes the step of administering a pharmacologically effective amount of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 to a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/01367

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07C217/86, C07C225/22, C07C233/43, C07C235/06, C07C255/46, C07C255/59, A61K31/135, A61K31/165, A61K31/275, A61K31/245
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07C217/86, C07C225/22, C07C233/43, C07C235/06, C07C255/46, C07C255/59, A61K31/135, A61K31/165, A61K31/275, A61K31/245

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COUTTS, Ian G. C.; HAMBLIN, Michael R., "Synthesis of spiroheterocycles by oxidative coupling of phenolic sulfonamides", J. Chem. Soc., Chem. Commun. (1980), (20), p.949-950	1-8, 10-11
A	JP, 2-76842, A (Fuji Photo Film Co., Ltd.), March 16, 1990 (16. 03. 90) & US, 5006660, A	1-8, 10-11
A	JP, 5-194400, A (Kumiai Chemical Industry Co., Ltd.), August 3, 1993 (03. 08. 93) & WO, 95/01339, A1	1-8, 10-11
A	JP, 7-41465, A (Sumitomo Pharmaceuticals Co., Ltd.), February 10, 1995 (10. 02. 95) (Family: none)	1-8, 10-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
June 19, 1998 (19. 06. 98)	June 30, 1998 (30. 06. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/01367

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 9, 12

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9 and 12 relate to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under the provision of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT,

2. [ ] Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/01367

Continuation of Box No. I of continuation of first sheet (1)

to search.

Form PCT/ISA/210 (extra sheet) (July 1992)